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(54) Title: PYRAZOLE CARBOXANILIDE FUNGICIDES		
(57) Abstract		Novel N-[2-(cyclic alkyl)phenyl]pyrazole-4-carboxamides useful as fungicides, methods of using said compounds, and fun- gicidal compositions containing them.

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PYRAZOLE CARBOXANILIDE FUNGICIDES

Field of the Invention

The present invention provides novel N-[2-(cyclic alkyl)phenyl]pyrazole-4-carboxamides useful as
5 fungicides.

Background of the Invention

Fungicides control various phytopathological diseases by interrupting various metabolic pathways within the fungal organism. Thus different fungicides
10 may control the same disease, but by different modes of action. Many organisms, however, can develop resistance to a particular mode of action over time. Thus, having available fungicides which act by various modes of action is important to adequately control most diseases.

One mode of action is the inhibition of the succinate dehydrogenase (SDH) enzyme in the respiratory pathway of fungi. This mode of action has previously been demonstrated for control of basidiomycetes. For example, carboxin is a commercially available fungicide
15 which exhibits this mode of action against various basidiomycetes. Drouhot et al. ["Properties of *Botrytis cinerea* Mitochondria and Effects of Various Toxicants Including Fungicides," Pesticide Science, 30:415-417, 1991] have suggested that such a mode of action for
20 control of ascomycetes, such as *Botrytis* sp., is needed to overcome resistance problems. In their tests of respiratory inhibition, carboxin exhibited a 68% inhibition at 1 μ M concentration and was judged the best fungicide of those tested for SDH mode of action against
25 *Botrytis*.
30

Pyrazolecarboxamide fungicides are known in the art. U.S. Patent Number 4,134,987 (Huppertz, January 16,

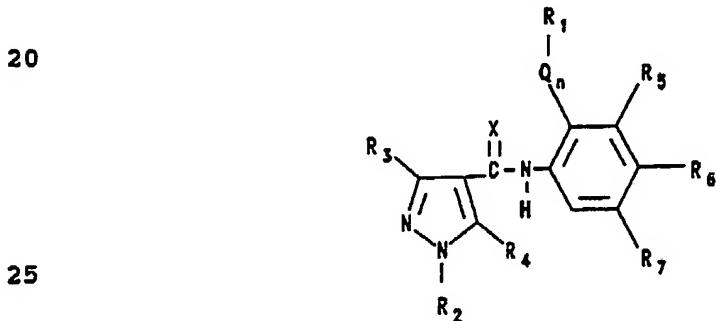
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1979) discloses various N-(phenyl)pyrazolecarboxamides. U.S. Patent Number 4,742,074, issued May 3, 1988, to Nishida et al., discloses various N-(substituted-indanyl)pyrazole-4-carboxamides useful as fungicides for 5 various agronomic diseases.

It is an object of this invention to provide compounds having a high level of activity in SDH inhibition in ascomycetes. It is a further object of this invention to provide compounds having a broad 10 spectrum of activity against fungal diseases of plants. It is a further object of this invention to provide methods of controlling or preventing fungal diseases of plants. It is a still further object of this invention to provide fungicidal compositions useful in carrying 15 out those methods.

Summary of the Invention

Therefore, the present invention comprises compounds of the formula:



wherein:

Q is C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl,
 $-(CH_2)_mCH=$, or $-(CH_2)_m-X-(CH_2)_m-$;

30 n is 0 or 1;
each m is independently 0, 1, 2, or 3;
each X is independently O or S;
R₁ is C3-C12 cycloalkyl, C3-C12 cycloalkenyl, C6-C12
bicycloalkyl, C3-C12 oxacycloalkyl, C3-C12
oxacycloalkenyl, C3-C12 thiacycloalkyl, C3-C12
thiacycloalkenyl, or C3-C12 cycloalkylamine, each
of which may be optionally substituted with one
or more C1-8 alkyl, C1-8 alkoxy, halo, or cyano

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- groups, provided that when $-Q-R_1$ is $-(CH_2)_mCH=R_1$,
the cycloalkyl of R_1 is a cycloalkylidene;
 R_2 is hydrogen, fluorinated methyl, methyl, ethyl, C2-C6
alkenyl, C3-C6 cycloalkyl, phenyl,
5 alkylthioalkyl, alkoxyalkyl, haloalkylthioalkyl,
 haloalkoxyalkyl, or hydroxyalkyl;
 R_3 is halomethyl, halomethoxy, methyl, ethyl, halo,
 cyano, methylthio, nitro, aminocarbonyl, or
 aminocarbonylmethyl;
10 R_4 is hydrogen, halo, or methyl;
 R_5 , R_6 , and R_7 are each independently selected from
hydrogen, halo, cyano, C1-6 alkyl, C2-C6 alkenyl,
C2-C6 alkynyl, C1-C4 alkoxy, C1-C4 alkylthio, C3-
C4 cycloalkyl, and halomethoxy.
15 The present invention also provides methods of
controlling or preventing fungal diseases of plants by
applying one or more compounds as just described to the
plant locus. The present invention also provides
fungicidal compositions comprising one or more of the
20 compounds just described and one or more adjuvants.
In the present invention it is preferred that n
is 0, R_2 is methyl, R_3 is fluorinated methyl, and R_4 is
hydrogen.
As used herein, the term "alkyl", unless
25 otherwise indicated, means an alkyl radical, straight or
branched chain, having, unless otherwise indicated, from
one to ten carbon atoms. The terms "alkenyl" and
"alkynyl" mean unsaturated radicals having from two to
six carbon atoms. Examples of such alkenyl groups
30 include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl,
2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 2-methyl-2-
propenyl, 1-methylethenyl, and the like. Examples of
such alkynyl groups include ethynyl, 1-propynyl,
2-propynyl, 1,1-dimethyl-2-propynyl, and so forth.
35 As used herein, the term "cycloalkyl" means a
cyclic alkyl radical having from three to twelve carbon
atoms. Examples of such cycloalkyl groups include
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclo-

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heptyl, cyclooctyl, and so forth. As used herein, the term "cycloalkenyl" means an unsaturated cyclic radical having from three to twelve carbon atoms. The radical may contain more than one double bond. Examples of such 5 cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and so forth.

As used herein, the term "bicycloalkyl" means a cyclic alkyl radical having from six to twelve carbon 10 atoms which comprise more than one ring structure. Examples of such cycloalkyl groups include norbornyl (bicyclo[2.2.1]heptyl).

As used herein, the terms "oxacycloalkyl" and "oxacycloalkenyl" mean cyclic alkyl and alkenyl radicals 15 having from three to twelve carbon atoms, one of which has been replaced by an oxygen. Examples are oxanyl, oxepanyl, oxocanyl, oxinyl, oxepinyl, oxocinyl, etc.

As used herein, the terms "thiacycloalkyl" and "thiacycloalkenyl" mean cyclic alkyl and alkenyl 20 radicals having from three to twelve carbon atoms, one of which has been replaced by a divalent sulfur atom. Examples are thianyl, thiepanyl, thiocanyl, thiinyl, thiepinyl, thiocinyl, etc.

As used herein, the term "cycloalkylamine" means 25 a cyclic alkyl radical having from three to twelve carbon atoms, one of which has been replaced by a divalent -NH- group forming a secondary amine or a divalent alkylamine group forming a tertiary amine. Examples are perhydroazinyl, perhydroazepinyl, 30 perhydroazocinyl, etc., and N-methylperhydroazinyl, N-methylperhydroazepinyl, N-methylperhydroazocinyl, etc.

As used herein, the term "alkoxy" means an alkyl group having, unless otherwise indicated, from one to six carbon atoms connected via an ether linkage. 35 Examples of such alkoxy groups include methoxy, ethoxy, propoxy, 1-methylethoxy, and so forth.

As used herein, the term "alkoxyalkyl" means an ether radical having, unless otherwise indicated, from

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one to ten carbon atoms. Examples of such alkoxyalkyl groups include methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, and so forth.

As used herein, the term "fluorinated methyl" means a methyl radical having one or more hydrogen atoms replaced by fluorine atoms, including radicals having all hydrogen atoms substituted by fluorine, i.e., fluoromethyl, difluoromethyl, and trifluoromethyl.

As used herein, the term "halo" means a radical selected from chloro, bromo, fluoro, and iodo. As used herein, the terms "halomethyl" or "halomethoxy" mean that one or more of the hydrogen atoms have been replaced by halogen atoms, including methyl or methoxy groups having all hydrogen atoms substituted with halogens. The term also includes mixed halogen substitution, for example, chlorodifluoromethyl.

As used herein, the term "alkylthioalkyl" means a thioether radical having, unless otherwise indicated, from one to ten carbon atoms. Examples of such alkylthioalkyl groups include methylthiomethyl, methylthioethyl, ethylthiomethyl, ethylthioethyl, and so forth.

Detailed Description of the Invention

Most of the compounds of the present invention may be easily prepared by coupling the desired 25 4-pyrazolecarbonyl chloride with the desired aniline. The following synthetic methods exemplify the ways in which the 4-pyrazolecarbonyl chloride compounds and the anilines may be prepared and coupled. Other compounds of the present invention may be derived from the 30 carboxanilides so prepared. The following abbreviations have the meanings shown:

	RT	room temperature
	RC	radial chromatography
	h	hour(s)
35	min	minute(s)
	DMSO	dimethylsulfoxide
	THF	tetrahydrofuran
	EtOAc	ethyl acetate

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Anilines

2-Cyclooctylaniline: Aniline (27.9 g, Aldrich), cyclooctene (33.0 g, Aldrich) and 'F-6' grade clay (9.2 g, Engelhard) were heated in a stirred autoclave for 10 5 h at 210 °C. The dark product was filtered and volatile materials were removed in vacuo (60 °C, 40 mm). The oil was distilled (Kugelrohr, 110-140 °C, 0.5 mm) to give 41.2 g of a viscous yellow oil. The product was chromatographed on silica (Waters 500 A, preparative liquid 10 chromatograph) with EtOAc and hexane to give 2-cyclooctylaniline as a viscous yellow oil (31.0 g).

The following 2-cycloalkylanilines were prepared as described above for 2-cyclooctylaniline. Appropriately substituted anilines and cycloalkenes were 15 commercially available (Aldrich) and used without additional purification.

20 2-cyclohexylaniline
 2-cyclopentylaniline
 2-cycloheptylaniline
 2-(exo)bicyclo[2.2.1]heptylaniline
 2-cyclohexyl-3-fluoroaniline
 2-cyclohexyl-4-fluoroaniline
 2-cyclohexyl-5-fluoroaniline
 2-cyclohexyl-3-methylaniline
 25 2-cyclohexyl-4-methylaniline
 2-cyclohexyl-5-methylaniline
 2-cyclopentyl-3,5-dimethylaniline
 2-cyclohexyl-5-methoxyaniline
 2-cyclooctyl-3-methoxyaniline
 30 2-cyclooctyl-5-methoxyaniline
 2-(1-methylcyclopentyl)aniline
 2-(1-methylcyclohexyl)-4-fluoroaniline
 2-(3-methylcyclohexyl)aniline

35 2-(1-Methylcyclopentyloxy)aniline: Sodium hydride (4.0 g, 60% oil dispersion, Aldrich) was rinsed three times with dry hexane under nitrogen. Diglyme (40 mL, anhydrous, Aldrich) was added. The slurry was

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rapidly stirred at RT and 1-methylcyclopentanol was added dropwise. The slurry was warmed to 80 °C for 30 min then cooled to RT. 2-Fluoronitrobenzene (14.1 g) was added, and the mixture was heated at reflux for 2 h.

- 5 The product was extracted with ether. The ether phase was washed with water, dried with brine, separated, and dried over K₂CO₃. The solution was filtered and concentrated in vacuo to give a light yellow oil. 2-(1-Methylcyclopentyloxy)nitrobenzene was distilled
10 (Kugelrohr, 100 °C, 0.5 mm) following distillation of diglyme to give a light yellow oil (21.0 g). The nitro compound was dissolved in ethanol (20 mL, absolute) and 5% Pd on charcoal (0.1 g) was added. The slurry was shaken on a Parr hydrogenation apparatus at 40 psi
15 hydrogen for 16 h. The sample was filtered and concentrated to give the aniline.

The following 2-cycloalkoxyanilines or 2-cycloalkylthioanilines were prepared as described above for 2-(1-methylcyclopentyl)oxyaniline from commercially
20 available alcohols or thiols.

- 2-(cyclohexyloxy)aniline
2-(cyclopentylmethoxy)aniline
2-(2-cyclopentylethoxy)aniline
2-(3-cyclopentylpropoxy)aniline
25 2-(cyclobutylmethoxy)aniline
2-(cyclohexylthio)aniline
2-(cyclohexyloxy)-5-methylaniline
2-[(exo)-bicyclo[2.2.1]heptyloxy]aniline
2-[(endo)-bicyclo[2.2.1]heptyloxy]aniline
30

The following 2-cycloalkoxyanilines were prepared as described above for 2-(1-methylcyclopentyloxy)aniline from commercially available diasteriomic mixtures of alcohols. The diasteriomers were separated via chromatography on silica (Waters 500 A, preparative liquid chromatograph) with EtOAc and hexane. Stereochemical assignments were based upon coupling constants in the proton NMR in CDCl₃.

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2-(4-methylcyclohexyloxy)aniline
2-(2,6-dimethylcyclohexyloxy)aniline

2-(1-Cyclopentylideneethyl)aniline and 2-(1-

5 cyclopentylethenyl)aniline: To a stirred solution of 2-acetylaniline (27.2 g, Aldrich) in ether at 0 °C was added cyclopentylmagnesium chloride (205 mL, 2.0 M in ether, Aldrich). The yellow solution was stirred overnight while warming to RT. Water was carefully added, 10 and the product was extracted with several portions of ether. The combined ether materials were dried with MgSO₄, filtered and concentrated in vacuo. Distillation (Kugelrohr, 130 °C, 0.5 mm) gave the alcohol (24.3 g) as a thick amber oil. The alcohol (15.1 g) was stirred 15 with DMSO (100 mL, anhydrous, Aldrich) at reflux for 4 h. The solution was cooled and the products extracted with ether and hexanes. The organic extracts were washed with water, saturated NaHCO₃ and brine, then dried with MgSO₄. The solution was filtered and concentrated in vacuo. The olefinic products were obtained as 20 a 3:2 ratio of 2-(1-cyclopentylideneethyl)aniline and 2-(1-cyclopentylethenyl)aniline. Chromatography on silica (Waters 500A, preparative liquid chromatograph) with EtOAc and hexane failed to separate the mixture and 25 gave the products as a clear, light yellow oil (8.94 g). The mixture was used directly for formation of carboxanilide products which were then separated.

2-(1-Cyclohexenyl)aniline: To cyclohexanone

30 (24.4 mL) and 2,6-di-t-butyl-4-methylpyridine (48.3 g) in CH₂Cl₂ (700 mL) at 0 °C was added dropwise triflic anhydride (42 mL) in CH₂Cl₂ (100 mL). The mixture was stirred overnight slowly coming to RT. A white solid was filtered and the filtrate was concentrated in vacuo. 35 The residue was triturated with hexanes and filtered. The filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexanes to give O-trifluoromethylsulfonyl-1-cyclohexenol.

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To N-Boc-aniline (30.8 g) in THF (300 mL) at -78 °C was added dropwise t-butyl lithium (1.7 M in pentane, 226 mL). The mixture was warmed to -22 °C for 2 h and cooled back down to -78 °C. Trimethyltin chloride (67.4 g) in THF (200 mL) was added dropwise. The reaction mixture was stirred overnight, slowly coming to RT, and then partitioned between ether and ice water. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% EtOAc/hexanes.

O-Trifluoromethylsulfonyl-1-cyclohexenol (6.9 g), prepared above, triphenylarsine (0.77 g), tris(dibenzylideneacetone)dipalladium (0.28 g), and N-Boc-(2-trimethyltin)aniline (10.7 g) were mixed in 15 N-methylpyrrolidinone (100 mL) and stirred overnight. The reaction mixture was then washed with water (2 x 100 mL), stirred with saturated aqueous KF (150 mL) for 0.5 h, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 5% 20 EtOAc/hexanes, to give N-Boc-2-(1-cyclohexenyl)aniline.

To N-Boc-2-(1-cyclohexenyl)aniline (15 g) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise trifluoroacetic acid (15 mL). The mixture was stirred overnight coming to RT and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and water while adjusting the aqueous layer to pH 9 with 2.5N NaOH. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated *in vacuo* leaving an oil (10.3 g) which was distilled (Kugelrohr) at 75 - 85 °C (0.25 mm) to give pure 2-(1-cyclohexenyl)aniline as a 30 clear colorless oil (8.6 g).

The following were prepared as described above using the appropriate ketone starting material:

- 2-(1-cyclopentenyl)aniline
- 2-(1-cycloheptenyl)aniline
- 35 2-(1-cyclooctenyl)aniline
- 2-(2-methyl-1-cyclopentenyl)aniline
- 2-(5,5-dimethyl-1-cyclopentenyl)aniline
- 2-(2,6-dimethyl-1-cyclohexenyl)aniline

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- 2-(3,3,5,5-tetramethyl-1-cyclohexenyl)aniline
2-(4-ethyl-1-cyclohexenyl)aniline
2-{2-[(1-methyl)ethyl]-1-cyclohexenyl}aniline
2-[6-[(1-methyl)ethyl]-1-cyclohexenyl]aniline
5 2-[4-[(1,1-dimethyl)ethyl]-1-cyclohexenyl]aniline
2-(6-ethyl-2-methyl-1-cyclohexenyl)aniline
2-{6-[(1,1-dimethyl)ethyl]-1-cyclohexenyl}aniline
2-(5,6-dihydro-2H-pyran-4-yl)aniline
2-(5,6-dihydro-2H-thiopyran-4-yl)aniline
10 2-(3-methyl-1-cyclopenten-1-yl)aniline
2-(4-methyl-1-cyclopenten-1-yl)aniline

2-[[4-(1,1-dimethyl)ethyl]cyclohexyl]aniline:

- 2-{{4-(1,1-dimethyl)ethyl}-1-cyclohexenyl}aniline (3 g),
15 prepared as above, platinum oxide (200 mg), glacial
acetic acid (1 mL), and ethanol (50 mL) were shaken on a
Parr hydrogenation apparatus under 60 lbs of hydrogen
overnight. Contents were filtered and the filtrate was
concentrated in vacuo leaving an oil (2.8 g). The oil
20 was purified by chromatography on silica gel eluting
with 7.5 % EtOAc/hexanes, to give pure 2-{{4-(1,1-
dimethyl)ethyl}cyclohexyl}aniline. Earlier fractions
were enriched in the trans isomer and later fractions
were enriched in the cis isomer.

25 Also prepared by this method was:

2-[(3,3,5,5-tetramethyl)-1-cyclohexyl]aniline

2-(Cyclohexylidenemethyl)aniline: To a slurry of
cyclohexyl triphenylphosphonium bromide (16.6 g) in THF
30 (100 mL) at 24 °C was added potassium t-butoxide (4.38
g). The mixture was stirred for 30 min.
o-Nitrobenzaldehyde (3.93 g) in THF (50 mL) was added
dropwise below 30 °C and stirred for 30 min. The
mixture was then partitioned between EtOAc and ice
35 water. The EtOAc layer was washed well with water,
dried ($MgSO_4$) and concentrated in vacuo. The residue
was chromatographed on silica gel with 5% EtOAc/hexanes
to give 1-(cyclohexylidenemethyl)-2-nitrobenzene.

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To 1-(cyclohexyldenemethyl)-2-nitrobenzene (1.6 g) in glacial acetic acid (50 mL), at 85 °C, was added iron powder (2.07 g). The mixture was refluxed for 15 min. The mixture was cooled and filtered through clay.

- 5 The filtrate was partitioned between EtOAc and ice water. The ethyl acetate layer was washed well with a saturated NaHCO₃ solution, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexanes to give 2-(cyclohexyldenemethyl)aniline.

The following 2-(cycloalkyldenemethyl)anilines were prepared as described above:

2-(cycloheptyldenemethyl)aniline

2-(cyclopentyldenemethyl)aniline

- 15 In the preparation of 1-(cyclopentyldenemethyl)-2-nitrobenzene, its isomer, 1-[(cyclopent-1-enyl)methyl]-2-nitrobenzene, was also isolated and then converted to 2-[(cyclopent-1-enyl)methyl]aniline.

- 20 2-(Cyclohexylmethyl)aniline: 1-(Cyclohexyldene-methyl)-2-nitrobenzene (3.45 g), prepared as above, glacial acetic acid (30 mL), ethanol (50 mL), and a catalytic amount of 10%Pd/C were shaken on a Parr Hydrogenator under an atmosphere of hydrogen at 23 °C for 24 h. The mixture was filtered through clay and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 10% EtOAc/hexanes to give 2-(cyclohexylmethyl)aniline.

- 25 The following 2-(cycloalkylmethyl)anilines were prepared as described above:

2-(cycloheptylmethyl)aniline

2-(cyclopentylmethyl)aniline

- 30 5-Chloro-2-cyclohexylaniline: To 1-chloro-4-cyclohexylbenzene (1.7 g) in H₂SO₄ (10 mL) at 20 °C was added HNO₃ (2.5 g) in H₂SO₄ (10 mL) maintaining the temperature below 30 °C. The mixture was allowed to stir for 1 h and then partitioned between CH₂Cl₂ and

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water. The CH_2Cl_2 layer was washed well with a saturated NaHCO_3 solution, dried (MgSO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 5% EtOAc/hexanes to give 5-chloro-2-
5 cyclohexyl-1-nitrobenzene. This compound was then reduced with iron powder as described above to yield the desired compound.

2-Cyclohexyl-3,5-dibromoaniline: To 4-
10 cyclohexylaniline (10 g), CuBr (9.4 g) and CuBr_2 (20.9 g) in acetonitrile (200 mL) was added dropwise a 90% *t*-butyl nitrite solution (16.9 mL) at 30 °C. The mixture was stirred for 1 h and concentrated *in vacuo*. The residue was taken up in EtOAc and washed with 10% HCl, dried (MgSO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with hexanes to give a mixture of 4-bromo-1-cyclohexylbenzene and
15 1-cyclohexyl-2,4-dibromobenzene.

To this mixture (2.8 g) in H_2SO_4 (18 mL) at 20 °C
20 was added HNO_3 (11.8 mL) in H_2SO_4 (11.8 mL) maintaining the temperature below 30 °C. The mixture was allowed to stir for 1 h and then partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed well with a saturated NaHCO_3 solution, dried (MgSO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel
25 eluting with hexanes to give 2-cyclohexyl-3,5-dibromo-1-nitrobenzene. This compound was then reduced with iron powder as described above to yield the desired compound.

30

Pyrazoles

Ethyl 3-cyano-1-methyl-1-H-pyrazole-4-carboxylate: To ethyl 3-(carboxaldehyde)-1-methyl-1-H-pyrazole-4-carboxylate, (7.8 g) in ethanol at 0 °C was added hydroxylamine hydrochloride (3.3 g). The material
35 was concentrated *in vacuo*; chloroform was added and removed *in vacuo* to assure removal of all of the ethanol. The white-yellow solid was stored under vacuum at RT. A slurry was formed in CH_2Cl_2 (150 mL,

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anhydrous). The slurry was cooled to 0 °C and pyridine (10.4 mL) was added followed by the careful addition of trifluoroacetic anhydride (15.7 mL). The solution was stirred 1 h at RT, then 3 h at reflux. The product was extracted with CH₂Cl₂. The organic material was washed with saturated NaHCO₃ and brine then separated and dried with MgSO₄. Filtration and concentration in vacuo gave the crude product (7.4 g). Chromatography on silica with hexane, EtOAc, and CH₂Cl₂ afforded the desired product (3.1 g).

Ethyl 3-(trifluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate: To ethyl 2-(ethoxymethylene)-4,4,4-trifluoromethyl acetoacetate (132 g, prepared according to JACS 73: 3684, 1951) in ethanol (600 mL) at 0 °C, 15 methyl hydrazine (29 mL) in ethanol (100 mL) was slowly added dropwise. After addition was complete, the contents were heated at reflux for 2 h. Stirring continued overnight while the contents cooled to RT. The yellow precipitate was filtered to give the pure desired 20 product (21 g). The filtrate was concentrated in vacuo leaving a yellow oil (81.6 g). The oil was distilled (Kugelrohr 50 °C, 0.025 mm) to give the N-methyl isomer of the desired compound (30 g) as a yellow oil. The distillation was continued (80 °C, 0.025 mm) to give 25 additional desired product as a yellow solid (35.8 g).

The following 1H-pyrazole-4-carboxylic acid esters were prepared as described above. The appropriate ethyl 2-(ethoxymethylene)acetoacetates were prepared as described in JACS, 73: 3684, 1951, using the 30 appropriate commercially available ethyl acetoacetates.

Ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate

Ethyl 1,3-dimethyl-1H-pyrazole-4-carboxylate

Ethyl 3-(difluoromethyl)-1H-pyrazole-4-carboxylate

35 Ethyl 1,3,5-trimethyl-1H-pyrazole-4-carboxylate

Ethyl 3-(chlorodifluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate

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Ethyl 1,5-dimethyl-3-trifluoromethyl-1H-pyrazole-4-carboxylate

Ethyl 3-(difluoromethyl)-1-(2-propenyl)-1H-pyrazole-4-carboxylate:

- 5 To a solution of potassium hydroxide (3.5 g) in ethanol (50 mL) at 0 °C was added dropwise the ethyl ester of 3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (10.1 g) in ethanol (50 mL), followed by dropwise addition of allyl bromide (4.6 mL).
- 10 The mixture was stirred overnight, partitioned between ether and 2N HCl. The ether layer was dried ($MgSO_4$) and concentrated in vacuo leaving an oil (11.4 g). The oil was distilled (Kugelrohr 80-85 °C, 0.3 mm) to give the isomer of the desired product as an oil (2.6 g).
- 15 Distillation was continued (100-105 °C, 0.3 mm) to give the desired compound as a clear colorless oil (8.0 g).

Ethyl 3-(methylthio)-1-methyl-1H-pyrazole-4-carboxylate:

- To the ethyl ester of 3-amino-1-methyl-1H-pyrazole-4-carboxylic acid (10 g, prepared as in U.S. Patent No. 3,098,075) and methyl disulfide (7.5 mL) in CH_3CN (80 mL) was added dropwise t-butyl nitrite in CH_3CN (20 mL). The contents were stirred overnight and partitioned between water and ether. The ether layer was dried ($MgSO_4$) and concentrated in vacuo leaving an amber solid (13.5 g). The solid was recrystallized from EtOAc/hexanes to give the desired ester as a light amber solid (8.0 g).

Ethyl 3-bromo-1-methyl-1H-pyrazole-4-carboxylate

- was prepared as described above for ethyl 3-(methylthio)-1-methyl-1H-pyrazole-4-carboxylate using copper(II) bromide.

Ethyl 3-chloro-1-methyl-1H-pyrazole-4-carboxylate

- was prepared as described above for ethyl 3-(methylthio)-1-methyl-1H-pyrazole-4-carboxylate using copper(II) chloride.

Ethyl 3-iodo-1-methyl-1H-pyrazole-4-carboxylate

- was prepared as described above for ethyl 3-(methylthio)-1-methyl-1H-pyrazole-4-carboxylate using copper(II) iodide.

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thio)-1-methyl-1H-pyrazole-4-carboxylate using iodine in place of methyl disulfide.

Ethyl 1,3-bis-(difluoromethyl)-1H-pyrazole-4-carboxylate:

5 carboxylate: Into a solution of ethyl 3-(difluoromethyl)-1H-pyrazole-4-carboxylate (5.6 g) in DMF (200 mL) at 0 °C was bubbled chlorodifluoromethane (26 g). Sodium hydroxide (50%, 24 g) was added dropwise. The contents were stirred overnight coming to RT and partitioned between water and EtOAc. The EtOAc layer was dried ($MgSO_4$) and concentrated in vacuo leaving a light amber oil (5.3 g). Chromatography on silica gel, eluting with a 15% EtOAc/hexanes mixture gave the desired compound in a pure form as a colorless oil (2.1 g).

Ethyl 3-(difluoromethoxy)-1-methyl-1H-pyrazole-4-carboxylate: Into a solution of ethyl 3-hydroxy-1-methyl-1H-pyrazole-4-carboxylate (10.0 g), prepared as above, in DMF (100 mL) at 0 °C was bubbled chlorodifluoromethane (50 g). At 0 °C, NaOH (50%, 48 g) was added dropwise and stirred 72 h, coming to RT. The mixture was partitioned between EtOAc and water. The EtOAc layer was dried ($MgSO_4$) and concentrated in vacuo leaving a yellow oil (7.9 g). The oil was chromatographed on silica gel eluting with 40% EtOAc/hexanes to give the desired compound as a light amber oil which solidified (3.4 g).

1-Methyl-3-nitro-1H-pyrazole-4-carboxylic acid:

To 3-amino-1-methyl-1H-pyrazole-4-carboxamide (4.6 g), 30 prepared according to *Helv Chim Acta* 42:349 (1959), and sodium nitrite (3.5 g) was added rapidly conc HCl (19 mL). Contents were refluxed 1 h, allowed to cool, and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated in vacuo leaving the desired compound 35 as a light yellow solid (900 mg).

3-(Trifluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid: Ethyl 3-(trifluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate (22.3 g) was added to a solution

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of sodium hydroxide (4.4 g) in methanol (200 mL). The contents were heated at reflux for 1 h, then cooled and stirred overnight. The contents were concentrated in vacuo and diluted with water. The aqueous solution was 5 made acidic with 2N HCl and the precipitated white solid was filtered to give the desired acid (18.2 g).

The following were prepared as described above using the appropriate pyrazole ester:

- 3-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic
10 acid
1,3-Dimethyl-1H-pyrazole-4-carboxylic acid
1,3,5-Trimethyl-1H-pyrazole-4-carboxylic acid
3-(Difluoromethyl)-1-(2-propenyl)-1H-pyrazole-4-
carboxylic acid
15 3-(Methylthio)-1-methyl-1H-pyrazole-4-carboxylic acid
3-Bromo-1-methyl-1H-pyrazole-4-carboxylic acid
3-Cyano-1-methyl-1H-pyrazole-4-carboxylic acid
3-Chloro-1-methyl-1H-pyrazole-4-carboxylic acid
3-Iodo-1-methyl-1H-pyrazole-4-carboxylic acid
20 3-Methoxy-1-methyl-1H-pyrazole-4-carboxylic acid
3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid
1,3-Bis(difluoromethyl)-1H-pyrazole-4-carboxylic acid
3-(Difluoromethoxy)-1-methyl-1H-pyrazole-4-carboxylic
acid
25 3-(Chlorodifluoromethyl)-1-methyl-1H-pyrazole-4-
carboxylic acid
1,5-Dimethyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic
acid
30 5-Chloro-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxaldehyde: To ethyl 4,4,4-trifluoroacetoacetate (18 mL, Aldrich) in ethanol (200 mL) was added methyl hydrazine (6.6 mL) in ethanol (50 mL). The mixture was refluxed for 16 h and concentrated in vacuo leaving a
35 white solid. Recrystallization from EtOAc/toluene (50:50) gave pure 5-hydroxy-1-methyl-3-trifluoromethyl-1H-pyrazole.

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DMF (106 mL) was stirred under N₂ while cooling in an ice/salt bath to 0 °C. POCl₃ (364 mL) was added dropwise at a rate such that the temperature did not rise above 10 °C. The mixture was then stirred at 0 °C
5 briefly and 5-hydroxy-1-methyl-3-(trifluoromethyl)-1H-pyrazole (106 g) was added with constant stirring. The mixture was stirred while slowly heating to 90 °C. As the temperature approached 90 °C the reaction became exothermic and HCl gas evolved. The temperature rose to
10 reflux. After the exotherm subsided the mixture was heated at gentle reflux for 16 h. The dark amber solution was cooled to RT and then poured onto 3 kg ice with stirring. The mixture was mixed thoroughly with the ice and more ice added to maintain the temperature
15 below 5 °C. The resulting slurry was stirred continuously for 4 h with occasional addition of ice to maintain low temperature. The solid was separated from the liquid phase by drawing the aqueous phase through a sintered glass filter tube. The solid was reslurried
20 with water (4 x 1 L) and then collected by filtration and air dried. The product was recrystallized from hexane which gave the desired compound as white needles (137 g). m.p. 39-41 °C. An additional 30 g product was obtained by concentration of the mother liquor.

25 The following pyrazolecarboxaldehydes were prepared as just described:

5-Chloro-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxaldehyde

5-Chloro-1,3-dimethyl-1H-pyrazole-4-carboxaldehyde

30

5-Fluoro-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxaldehyde: A suspension of anhydrous KF (4 g) in anhydrous DMF (20 mL) was stirred under N₂ and 1-methyl-3-trifluoromethyl-5-chloropyrazole-4-carboxaldehyde

35 (10.6 g) added. The mixture was heated at 150 °C for 6 h. The mixture was poured onto ice (250 g) and was mixed thoroughly. The mixture was extracted with ether (5 X 50 mL). The ether solution was dried (MgSO₄) and

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concentrated in vacuo leaving an amber liquid (10 g). The liquid was distilled under reduced pressure to give one fraction, 8.0 g yellow liquid b.p. 68-74 °C @ 0.4 Torr.

- 5 The following pyrazolecarboxaldehydes were prepared as described above:

3-Difluoromethyl-5-fluoro-1-methyl-1H-pyrazole-4-carboxaldehyde

1,3-Dimethyl-5-fluoro-1H-pyrazole-4-carboxaldehyde

10

1-Methyl-3-trifluoromethyl-5-fluoro-1H-pyrazole-4-carboxylic acid: A solution of 1-methyl-3-

trifluoromethyl-5-fluoro-pyrazole-4-carboxaldehyde (9.8 g) in acetone (60 mL) was stirred rapidly at RT while a 15 solution of potassium dichromate dihydrate (5.6 g) in water (38 mL) and sulfuric acid (4.6 mL) was added. The mixture was stirred rapidly overnight then diluted with water (150 mL). The mixture was extracted with CH₂Cl₂ (6 x 75mL). The combined organic solution was washed with 20 water, dried (MgSO₄), filtered and concentrated in vacuo leaving a light yellow solid (7.2 g). The solid was recrystallized from EtOAc/hexane to give the desired compound as white crystals (3.8 g). m.p. 165-166 °C.

By this method the following pyrazolecarboxylic acids were prepared from the pyrazolecarboxaldehydes 25 described above:

5-Chloro-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid

5-Chloro-1,3-dimethyl-1H-pyrazole-4-carboxylic acid

30 3-Difluoromethyl-5-fluoro-1-methyl-1H-pyrazole-4-carboxylic acid

1,3-Dimethyl-5-fluoro-1H-pyrazole-4-carboxylic acid

35 1-Methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid chloride: 3-(Trifluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (21 g) and thionyl chloride (75 mL) were heated at reflux for 1.5 h. The

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contents were concentrated in vacuo leaving the desired acid chloride as a yellow oil.

This method was used to prepare the acid chloride of each of the pyrazole-4-carboxylic acids prepared 5 above.

3-(Difluoromethyl)-1H-pyrazole-4-carboxylic acid:

The ethyl ester of 3-(difluoromethyl)-1H-4-carboxylic acid (10 g) and freshly distilled trimethylsilyl iodide 10 (25 mL) were heated at 90 °C for 4 h. After cooling, the contents were partitioned between ether and ice water. The ether layer was washed with aqueous sodium meta-bisulfite, dried ($MgSO_4$), and concentrated in vacuo leaving the desired white solid (8 g).

15

Pyrazole-Aniline Coupling

N-(2-Cyclohexylphenyl)-1-methyl-3-(trifluoro-methyl)-1H-pyrazole-4-carboxamide: To 1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid chloride 20 (1.6 g) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise a solution of 2-cyclohexylaniline (1.3 g) and triethyl-amine (1.0 mL) in CH_2Cl_2 (25 mL). The contents were stirred overnight, coming to RT. The contents were washed with water, 2N HCl (2x100 mL), dried ($MgSO_4$) and 25 concentrated in vacuo leaving an amber foam (2.9 g). Crystallization from EtOAc/hexane gave the desired amide as white crystals (1.2 g). Most of the compounds of the present invention were made via this coupling procedure.

N-(2-Cyclohexylphenyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide: 3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (2.0 g) and 1,1'-carbonyldiimidazole 30 (2.0 g) were mixed in THF (20mL, anhydrous) and stirred for 1 h. 2-Cyclohexylaniline (2.2 g) was added, and the contents were heated at reflux for 2 h. After cooling 35 to RT, the contents were concentrated in vacuo leaving a foam (3.7 g). The foam was chromatographed on silica gel (Waters Prep 500) eluting with EtOAc and hexanes to give the desired amide as a white foam (750 mg). The

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foam was crystallized from EtOAc /pentane to give the product as a white solid (510 mg).

Thioamides

- 5 N-(2-Cyclohexylphenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbothioamide: N-(2-cyclohexylphenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (2.0 g) and Lawesson's reagent (2.4 g) were refluxed in toluene (100 mL) for 1 h.
- 10 Contents were stirred overnight at RT and filtered. The filtrate was concentrated in vacuo leaving a yellow solid which was chromatographed on silica gel eluting with 35% EtOAc/hexanes to give a yellow solid. The solid was recrystallized from EtOAc to give the desired
- 15 compound as a yellow solid (1.1 g).

By this method the following carbothioamides were prepared from the corresponding carboxamides:

- 15 N-(2-Cycloheptylphenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carbothioamide
- 20 N-(2-Bicyclo[2.2.1]hept-2-ylphenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbothioamide, exo-
N-(2-Bicyclo[2.2.1]hept-2-ylphenyl)-3-chloro-1,5-dimethyl-1-methyl-1H-pyrazole-4-carbothioamide,
exo-

25

Other Compounds

- 20 N-[2-(1-cyclopentylethyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide: A mixture of N-[2-(1-cyclopentylideneethyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide and N-[2-(1-cyclopentylethenyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (2.5 g), each prepared using the methods described above, were shaken on a Parr Shaker with 5% Pd/C in ethanol (75 mL) under 60 lbs of H₂ overnight. Contents were filtered and concentrated in vacuo leaving a white solid (2.44 g). The solid was recrystallized from EtOAc/hexanes to give the desired compound as a white solid (1.3 g).

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The following examples of compounds of the present invention were prepared using the methods described above and used in the biological assays described below:

5

	<u>Example No.</u>	<u>Compound</u>	<u>Melting Pt. (°C)</u>
10	1	1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-3-(difluoromethyl)-1-methyl-	132-134
15	2	1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-1-methyl-3-(trifluoromethyl)-	120-122
20	3	1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-1,3-dimethyl-	182-184
25	4	1H-pyrazole-4-carboxamide, 3-cyano-N-(2-cyclohexylphenyl)-1-methyl-	161-163
30	5	1H-pyrazole-4-carboxamide, 3-bromo-N-(2-cyclohexylphenyl)-1-methyl-	158-160
35	6	1H-pyrazole-4-carboxamide, N-(2-cyclopentylphenyl)-1,3-dimethyl-	150-152
40	7	1H-pyrazole-4-carboxamide, N-(2-cyclopentylphenyl)-3-(difluoromethyl)-1-methyl-	127-128
45	8	1H-pyrazole-4-carboxamide, N-(2-cyclopentylphenyl)-1-methyl-3-(trifluoromethyl)-	147-149
50	9	1H-pyrazole-4-carboxamide, N-(2-cycloheptylphenyl)-3-(difluoromethyl)-1-methyl-	116-117

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| 10 | 1H-pyrazole-4-carboxamide, N-(2-cycloheptylphenyl)-1-methyl-3-(trifluoromethyl)- | 131-132 |
| 5 | 11 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-4-fluorophenyl)-3-(difluoromethyl)-1-methyl- | 135-137 |
| 10 | 12 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-4-fluorophenyl)-1-methyl-3-(trifluoromethyl)- | 171-172 |
| 15 | 13 1H-pyrazole-4-carboxamide, N-(2-cycloheptylphenyl)-1,3-dimethyl- | 137-139 |
| 20 | 14 1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-3-(difluoromethyl)-1-(2-propenyl)- | 129-131 |
| 25 | 15 1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-3-(difluoromethyl)- | 138-140 |
| 30 | 16 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-5-fluorophenyl)-3-(difluoromethyl)-1-methyl- | 139-141 |
| 35 | 17 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-3-fluorophenyl)-3-(difluoromethyl)-1-methyl- | 141-143 |
| 40 | 18 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-5-methylphenyl)-1-methyl-3-(trifluoromethyl)- | 146-147 |
| 45 | 19 1H-pyrazole-4-carboxamide, N-(2-cyclohexyl-3-methylphenyl)-1-methyl-3-(trifluoromethyl)- | 178-179 |

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- 20 1H-pyrazole-4-carboxamide, N-(2- 157-159
cyclohexyl-3-methylphenyl)-3-
(difluoromethyl)-1-methyl-
- 5 21 1H-pyrazole-4-carboxamide, N-(2- 128-129
cyclohexyl-5-methylphenyl)-3-
(difluoromethyl)-1-methyl-
- 10 22 1H-pyrazole-4-carboxamide, N-[2- 125-126
(cyclohexyloxy)phenyl]-3-
(difluoromethyl)-1-methyl-
- 15 23 1H-pyrazole-4-carboxamide, N-[2- 128-129
(cyclohexyloxy)phenyl]-1-methyl-3-
(trifluoromethyl)-
- 20 24 1H-pyrazole-4-carboxamide, N-(2- 105-107
cyclooctylphenyl)-3-
(difluoromethyl)-1-methyl-
- 25 25 1H-pyrazole-4-carboxamide, N-(2- 100-102
cyclooctylphenyl)-1-methyl-3-
(trifluoromethyl)-
- 25 26 1H-pyrazole-4-carboxamide, N-(2- 129-130
bicyclo[2.2.1]hept-2-ylphenyl)-3-
(difluoromethyl)-1-methyl-, exo-
- 30 27 1H-pyrazole-4-carboxamide, N-(2- 171-173
bicyclo[2.2.1]hept-2-ylphenyl)-1-
methyl-3-(trifluoromethyl)-, exo-
- 35 28 1H-pyrazole-4-carboxamide, N-(2- 171-172
cyclohexyl-4-methylphenyl)-3-
(difluoromethyl)-1-methyl-

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- 29 1H-pyrazole-4-carboxamide, N-(2- 179-180
cyclohexyl-4-methylphenyl)-1-
methyl-3-(trifluoromethyl)-
- 5 30 1H-pyrazole-4-carboxamide, N-(2- 144-146
cyclohexylphenyl)-1,3,5-trimethyl-
- 31 1H-pyrazole-4-carboxamide, N-(2- 146-148
cyclopentyl-3,5-dimethylphenyl)-1-
methyl-3-(trifluoromethyl)-
- 10 32 1H-pyrazole-4-carboxamide, N-(2- 143-145
cyclohexyl-5-methoxyphenyl)-1-
methyl-3-(trifluoromethyl)-
- 15 33 1H-pyrazole-4-carboxamide, N-[2-(1- 102-104
cyclopentylideneethyl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 20 34 1H-pyrazole-4-carboxamide, N-[2-(1- 122-124
cyclopentylethenyl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 25 35 1H-pyrazole-4-carboxamide, 3- 141-143
(difluoromethyl)-1-methyl-N-[2-(1-
methylcyclopentyloxy)phenyl]-
- 30 36 1H-pyrazole-4-carboxamide, 1- 142-144
methyl-N-[2-(1-
methylcyclopentyloxy)phenyl]-3-
(trifluoromethyl)-
- 37 1H-pyrazole-4-carboxamide, N-(2- 140-141
cyclooctyl-3-methoxyphenyl)-1-
methyl-3-(trifluoromethyl)-
- 35

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	38	1H-pyrazole-4-carboxamide, N-(2-cyclooctyl-5-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-	134-135
5	39	1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-1-methyl-3-(methylthio)-	120-122
10	40	1H-pyrazole-4-carboxamide, N-[2-(cyclohexylidenemethyl)phenyl]-1-methyl-3-(trifluoromethyl)-	93-94
15	41	1H-pyrazole-4-carboxamide, N-(2-cyclooctylphenyl)-1,3-dimethyl-	132-133
20	42	1H-pyrazole-4-carboxamide, N-[2-(cyclobutylmethoxy)phenyl]-3-(difluoromethyl)-1-methyl-	135-136
25	43	1H-pyrazole-4-carboxamide, N-[2-(cyclobutylmethoxy)phenyl]-1-methyl-3-(trifluoromethyl)-	111-112
30	44	1H-pyrazole-4-carboxamide, N-[2-(cyclohexylthio)phenyl]-3-(difluoromethyl)-1-methyl-	74-76
35	45	1H-pyrazole-4-carboxamide, N-[2-(cyclohexylthio)phenyl]-1-methyl-3-(trifluoromethyl)-	88-93
	46	1H-pyrazole-4-carboxamide, N-[2-(cyclopentylmethoxy)phenyl]-3-(difluoromethyl)-1-methyl-	118-120
	47	1H-pyrazole-4-carboxamide, N-[2-(cyclopentylmethoxy)phenyl]-1-methyl-3-(trifluoromethyl)-	97-99

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|----|----|---|---------|
| | 48 | 1H-pyrazole-4-carboxamide, N-[2-(3-cyclopentylpropoxy)phenyl]-3-(difluoromethyl)-1-methyl- | 114-115 |
| 5 | 49 | 1H-pyrazole-4-carboxamide, N-[2-(3-cyclopentylpropoxy)phenyl]-1-methyl-3-(trifluoromethyl)- | 121-123 |
| 10 | 50 | 1H-pyrazole-4-carboxamide, 3-chloro-N-(2-cyclohexylphenyl)-1-methyl- | 167-169 |
| 15 | 51 | 1H-pyrazole-4-carboxamide, 3-chloro-N-(2-cycloheptylphenyl)-1-methyl- | 157-159 |
| 20 | 52 | 1H-pyrazole-4-carboxamide, N-(2-bicyclo[2.2.1]hept-2-ylphenyl)-3-chloro-1-methyl-, exo- | 152-154 |
| 25 | 53 | 1H-pyrazole-4-carboxamide, N-[2-(1-cyclopentylethyl)phenyl]-1-methyl-3-(trifluoromethyl)- | 133-135 |
| 30 | 54 | 1H-pyrazole-4-carboxamide, N-[2-(2-cyclopentylethoxy)phenyl]-3-(difluoromethyl)-1-methyl- | 101-104 |
| 35 | 55 | 1H-pyrazole-4-carboxamide, N-[2-(2-cyclopentylethoxy)phenyl]-1-methyl-3-(trifluoromethyl)- | 114-116 |
| | 56 | 1H-pyrazole-4-carboxamide, N-[2-(cyclohexyl)phenyl]-3-iodo-1-methyl- | 164-166 |

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| 57 | 1H-pyrazole-4-carboxamide, N-[2-(cycloheptyl)phenyl]-3-iodo-1-methyl- | 144-146 |
| 5 | 58 1H-pyrazole-4-carboxamide, N-(2-bicyclo[2.2.1]hept-2-ylphenyl)-3-iodo-1-methyl-, exo- | 141-142 |
| 10 | 59 1H-pyrazole-4-carboxamide, N-(2-(cyclohexylphenyl)-3-(difluoromethoxy)-1-methyl- | 130-132 |
| 15 | 60 1H-pyrazole-4-carboxamide, N-(2-(cycloheptylphenyl)-3-(difluoromethoxy)-1-methyl- | 139-140 |
| 20 | 61 1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-1,3-bis(difluoromethyl)- | 143-145 |
| 25 | 62 1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-1-methyl-3-nitro- | 173-175 |
| 30 | 63 1H-pyrazole-4-carboxamide, 3-bromo-N-(2-cycloheptylphenyl)-1-methyl- | 161-162 |
| 35 | 64 1H-pyrazole-4-carboxamide, 3-bromo-N-(2-cyclopentylphenyl)-1-methyl- | 130-132 |
| | 65 1H-pyrazole-4-carboxamide, N-(2-bicyclo[2.2.1]hept-2-ylphenyl)-3-bromo-1-methyl-, exo- | 129-131 |
| | 66 1H-pyrazole-4-carboxamide, N-(2-cycloheptylphenyl)-1,3,5-trimethyl- | 138-140 |

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| 67 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-(1-
methylcyclopentyl)phenyl]-3-
(trifluoromethyl)- | 152-154 |
| 5 | | |
| 68 | 1H-pyrazole-4-carboxamide, N-(2-
cyclooctylphenyl)-3-iodo-1-methyl- | 134-135 |
| 10 | | |
| 69 | 1H-pyrazole-4-carboxamide, N-(2-
cyclopentylphenyl)-3-iodo-1-methyl- | 147-149 |
| 15 | | |
| 70 | 1H-pyrazole-4-carboxamide,
1-methyl-N-[2-(3-methylcyclohexyl)-
phenyl]-3-(trifluoromethyl)-, | 113-115 |
| 20 | trans- | |
| 71 | 1H-pyrazole-4-carboxamide, N-(2-
bicyclo[2.2.1]hept-2-ylphenyl)-1,3-
dimethyl-, exo- | 162-164 |
| 25 | | |
| 72 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-[(4-
methylcyclohexyl)oxy]phenyl]-3-
(trifluoromethyl)-, cis- | 120-122 |
| 30 | | |
| 73 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-[(4-
methylcyclohexyl)oxy]phenyl]-3-
(trifluoromethyl)-, trans- | 136-138 |
| 35 | | |
| 74 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-[(2,6-
dimethylcyclohexyl)oxy]phenyl]-3-
(trifluoromethyl)-,
(1alpha,2alpha,6alpha)- | 117-119 |

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|------|--|----------------|
| 75 | 1H-pyrazole-4-carboxamide, 1- | 156-157 |
| | methyl-N-[2-[(2,6- | |
| | dimethylcyclohexyl)oxy]phenyl]-3- | |
| | (trifluoromethyl)-, | |
| 5 | (1alpha,2alpha,6beta)- | |
|
 | | |
| 76 | 1H-pyrazole-4-carboxamide, 1- | 121-122 |
| | methyl-N-[2-[(2,6- | |
| | dimethylcyclohexyl)oxy]phenyl]-3- | |
| 10 | (trifluoromethyl)-, | |
| | (1alpha,2beta,6beta)- | |
|
 | | |
| 77 | 1H-pyrazole-4-carbothioamide, N- | 202-204 |
| | (2-cyclohexylphenyl)-3- | |
| 15 | (difluoromethyl)-1-methyl | |
|
 | | |
| 78 | 1H-pyrazole-4-carbothioamide, N- | 147-149 |
| | (2-cycloheptylphenyl)-3- | |
| | (trifluoromethyl)-1-methyl | |
| 20 | | |
| 79 | 1H-pyrazole-4-carboxamide, 1- | 123-126 |
| | methyl-N-[2-(3- | |
| | methylicyclohexyl)phenyl]-3- | |
| | (trifluoromethyl)-, cis- | |
| 25 | | |
| 80 | 1H-pyrazole-4-carboxamide, N-[2- | 160 |
| | (bicyclo[2.2.1]hept-2-yloxy)- | |
| | phenyl]-3-(difluoromethyl)-1- | |
| | methyl-, exo- | |
| 30 | | |
| 81 | 1H-pyrazole-4-carboxamide, N-[2- | 141 |
| | (bicyclo[2.2.1]hept-2-yloxy)- | |
| | phenyl]-1-methyl-3- | |
| | (trifluoromethyl)-, exo- | |
| 35 | | |

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|----|---|---------|
| 82 | 1H-pyrazole-4-carboxamide, N-[2-(bicyclo[2.2.1]hept-2-yloxy)-phenyl]-3-(difluoromethyl)-1-methyl-, endo- | 127 |
| 5 | | |
| 83 | 1H-pyrazole-4-carboxamide, 3-(difluoromethyl)-1-methyl-N-[2-(1-methylcyclopentyl)phenyl]- | 152 |
| 10 | | |
| 84 | 1H-pyrazole-4-carboxamide, N-(2-cyclohexylphenyl)-5-fluoro-1-methyl-3-(trifluoromethyl)- | 146 |
| 15 | | |
| 85 | 1H-pyrazole-4-carboxamide, N-(2-bicyclo[2.2.1]hept-2-ylphenyl)-5-fluoro-1-methyl-3-(trifluoromethyl)-, exo- | 157-159 |
| 20 | | |
| 86 | 1H-pyrazole-4-carboxamide, N-(2-cycloheptylphenyl)-5-fluoro-1-methyl-3-(trifluoromethyl)- | 167-168 |
| 25 | | |
| 87 | 1H-pyrazole-4-carboxamide, 5-chloro-N-(2-cyclohexylphenyl)-1-methyl-3-(trifluoromethyl)- | 153-155 |
| 30 | | |
| 88 | 1H-pyrazole-4-carboxamide, N-(2-bicyclo[2.2.1]hept-2-ylphenyl)-5-chloro-1-methyl-3-(trifluoromethyl)-, exo- | 196-197 |
| 35 | | |
| 89 | 1H-pyrazole-4-carboxamide, 5-chloro-N-(2-cycloheptylphenyl)-1-methyl-3-(trifluoromethyl)- | 170-172 |
| 90 | 1H-pyrazole-4-carboxamide, 3-(chlorodifluoromethyl)-N-(2-cyclopentylphenyl)-1-methyl- | 143-145 |

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|----|--|---------|
| 91 | 1H-pyrazole-4-carboxamide, N-[2-
bicyclo[2.2.1]hept-2-ylphenyl]-3-
(chlorodifluoromethyl)-1-methyl-,
exo- | 156-157 |
| 5 | | |
| 92 | 1H-pyrazole-4-carboxamide, 3-
(chlorodifluoromethyl)-N-(2-
cycloheptylphenyl)-1-methyl- | 132-134 |
| 10 | | |
| 93 | 1H-pyrazole-4-carboxamide, N-(5-
chloro-2-cyclohexylphenyl)-3-
(difluoromethyl)-1-methyl- | 178-180 |
| 15 | | |
| 94 | 1H-pyrazole-4-carboxamide, N-(5-
chloro-2-cyclohexylphenyl)-1-
methyl-3-(trifluoromethyl)- | 165 |
| 20 | | |
| 95 | 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-N-[4-fluoro-2-(1-
methylcyclohexyl)phenyl]-1-methyl- | 169 |
| 25 | | |
| 96 | 1H-pyrazole-4-carboxamide, N-[2-
(cyclohexyloxy)-5-methylphenyl]-3-
(difluoromethyl)-1-methyl- | 126 |
| 97 | 1H-pyrazole-4-carboxamide, N-[2-
(cyclohexyloxy)-5-methylphenyl]-1-
methyl-3-(trifluoromethyl)- | 133 |
| 30 | | |
| 98 | 1H-pyrazole-4-carboxamide, N-[4-
fluoro-2-(1-methylcyclohexyl)-
phenyl]-1-methyl-3-
(trifluoromethyl)- | 203 |
| 35 | | |
| 99 | 1H-pyrazole-4-carboxamide, N-(2-
cycloheptylphenyl)-1,5-dimethyl-3-
(trifluoromethyl)- | 145 |

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- 100 1H-pyrazole-4-carboxamide, N-(2- 169
bicyclo[2.2.1]hept-2-ylphenyl)-1,5-
dimethyl-3-(trifluoromethyl)-, exo-
- 5 101 1H-pyrazole-4-carboxamide, N-(2- 117
cyclopentylphenyl)-1,5-dimethyl-3-
(trifluoromethyl)-
- 10 102 1H-pyrazole-4-carbothioamide, N- 213
(2-bicyclo[2.2.1]hept-2-ylphenyl)-
3-(difluoromethyl)-1-methyl-, exo-
- 15 103 1H-pyrazole-4-carbothioamide, N-(2- 117
bicyclo[2.2.1]hept-2-ylphenyl)-3-
chloro-1,5-dimethyl-, exo-
- 20 104 1H-pyrazole-4-carboxamide, 3- 130
(difluoromethyl)-N-[2-(5,6-dihydro-
2H-pyran-4-yl)phenyl]-1-methyl-
- 25 105 1H-pyrazole-4-carboxamide, 3- 113
chloro-N-(2-cycloheptylphenyl)-1,5-
dimethyl-
- 30 106 1H-pyrazole-4-carboxamide, N-(2- 138
bicyclo[2.2.1]hept-2-ylphenyl)-5-
chloro-1,3-dimethyl-, exo-
- 107 1H-pyrazole-4-carboxamide, 5- 147
chloro-N-(2-cycloheptylphenyl)-1,3-
dimethyl-
- 35 108 1H-pyrazole-4-carboxamide, N-[2- 170
(5,6-dihydro-2H-pyran-4-yl)phenyl]-
1-methyl-3-(trifluoromethyl)-

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- 109 1H-pyrazole-4-carboxamide, N-[2- 103
(1-cyclohexen-1-yl)phenyl]-3-
(difluoromethyl)-1-methyl-
- 5 110 1H-pyrazole-4-carboxamide, N-[2- 113
(1-cyclohexen-1-yl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 10 111 1H-pyrazole-4-carboxamide, N- 119
[2-(1-cyclohepten-1-yl)phenyl]-3-
(difluoromethyl)-1-methyl-
- 15 112 1H-pyrazole-4-carboxamide, N-[2- 107
(1-cyclohepten-1-yl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 20 113 1H-pyrazole-4-carboxamide, N-(2- 126-128
cycloheptylphenyl)-5-fluoro-1,3-
dimethyl-
- 114 1H-pyrazole-4-carboxamide, 5- 112-113
chloro-N-(2-cycloheptylphenyl)-3-
(difluoromethyl)-1-methyl-
- 25 115 1H-pyrazole-4-carboxamide, N-(2- 105-107
cycloheptylphenyl)-3-
(difluoromethyl)-5-fluoro-1-methyl-
- 30 116 1H-pyrazole-4-carboxamide, N-[2- 101-102
(cyclohexylidenemethyl)phenyl]-3-
(difluoromethyl)-1-methyl-
- 35 117 1H-pyrazole-4-carboxamide, N-[2- 123
(1-cyclopenten-1-ylmethyl)phenyl]-
3-(difluoromethyl)-1-methyl-

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- 118 1H-pyrazole-4-carboxamide, N-[2-
(cyclopentylidenemethyl)phenyl]3-
(difluoromethyl)-1-methyl- 115
- 5 119 1H-pyrazole-4-carboxamide, N-[2-
(1-cycloocten-1-yl)phenyl]-4-
(difluoromethyl)-1-methyl- 161
- 10 120 1H-pyrazole-4-carboxamide, N-[2-
(1-cycloocten-1-yl)phenyl]-1-
methyl-3-(trifluoromethyl)- 125
- 15 121 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-1-methyl-N-[2-
(3,3,5,5-tetramethyl-1-cyclohexen-
1-yl)phenyl]- 124
- 20 122 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-N-[2-(5,5-
dimethyl-1-cyclopenten-1-
yl)phenyl]-1-methyl- 117
- 25 123 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-(3,3,5,5-tetramethyl-
1-cyclohexen-1-yl)phenyl]-3-
(trifluoromethyl)- 115
- 30 124 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-N-[2-(2,6-
dimethyl-1-cyclohexen-1-yl)phenyl]-
1-methyl- 121
- 35 125 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-N-[2-(4-ethyl-1-
cyclohexen-1-yl)phenyl]-1-methyl- 124

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- 126 1H-pyrazole-4-carboxamide, N-[2- 111
(4-ethyl-1-cyclohexen-1-yl)phenyl]-
1-methyl-3-(trifluoromethyl)-
- 5 127 1H-pyrazole-4-carboxamide, N-[2- 116
(cyclopentylidenemethyl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 10 128 1H-pyrazole-4-carboxamide, N- 142
[2-[2-(1-methylethyl)-1-
cyclohexen-1-yl]phenyl]-1-methyl-3-
(trifluoromethyl)-
- 15 129 1H-pyrazole-4-carboxamide, N- 161
[2-(cyclohexylmethyl)phenyl]-3-
(difluoromethyl)-1-methyl-
- 20 130 1H-pyrazole-4-carboxamide, N-[2- 128
(cyclohexylmethyl)phenyl]-1-methyl-
3-(trifluoromethyl)-
- 25 131 1H-pyrazole-4-carboxamide, 1- Glass at
methyl-N-[2-[6-(1-methylethyl)-1- ambient temp.
cyclohexen-1-yl]phenyl]-3-
(trifluoromethyl)-
- 30 132 1H-pyrazole-4-carboxamide, 3- 156-157
(difluoromethyl)-N-[2-[4-(1,1-
dimethylethyl)-1-cyclohexen-1-
yl]phenyl]-1-methyl-
- 35 133 1H-pyrazole-4-carboxamide, N-[2- 155-156
[4-(1,1-dimethylethyl)-1-
cyclohexen-1-yl]phenyl]-1-methyl-3-
(trifluoromethyl)-

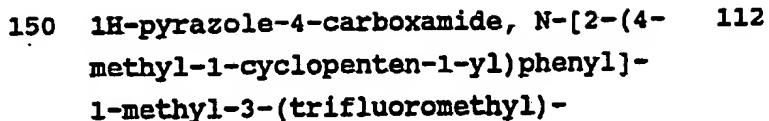
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- | | | |
|-----|--|---------------------------|
| 134 | 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-N-[2-[4-(1,1-
dimethylethyl)cyclohexyl]phenyl]-1-
methyl- | 152-154 |
| 5 | | |
| 135 | 1H-pyrazole-4-carboxamide, N-[2-
[4-(1,1-dimethylethyl)cyclohexyl]-
phenyl]-1-methyl-3-
(trifluoromethyl)- | 64-66 |
| 10 | | |
| 136 | 1H-pyrazole-4-carboxamide, N-
(3,5-dibromo-2-cyclohexylphenyl)-
1-methyl-3-(trifluoromethyl)- | 226-228 |
| 15 | | |
| 137 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-(2-methyl-1-
cyclopenten-1-yl)phenyl]-3-
(trifluoromethyl)- | 122.5-124 |
| 20 | | |
| 138 | 1H-pyrazole-4-carboxamide, N-
[2-(6-ethyl-2-methyl-1-cyclohexen-
1-yl)phenyl]-1-methyl-3-
(trifluoromethyl)- | 118.5-120.5 |
| 25 | | |
| 139 | 1H-pyrazole-4-carboxamide, 1-
methyl-N-[2-(3,3,5,5-
tetramethylcyclohexyl)phenyl]-3-
(trifluoromethyl)- | 147-149 |
| 30 | | |
| 140 | 1H-pyrazole-4-carboxamide, 3-
(difluoromethyl)-1-methyl-N-[2-
(3,3,5,5-tetramethylcyclohexyl)-
phenyl]- | 121.5-123.5 |
| 35 | | |
| 141 | 1H-pyrazole-4-carboxamide, N-[2-
[6-(1,1-dimethylethyl)-1-
cyclohexen-1-yl]phenyl]-1-methyl-3-
(trifluoromethyl)- | Glass at
ambient temp. |

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- 142 1H-pyrazole-4-carboxamide, N-[2- 150
(cyclopentylmethyl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 5 143 1H-pyrazole-4-carboxamide, N-[2- 106-107
(cycloheptylidene(methyl)phenyl]-1-
methyl-3-(trifluoromethyl)-
- 10 144 1H-pyrazole-4-carboxamide, 3- 115
(difluoromethyl)-N-[2-(5,6-dihydro-
2H-thiopyran-4-yl)phenyl]-1-methyl-
- 15 145 1H-pyrazole-4-carboxamide, 1- 132
methyl-N-[2-(cycloheptylmethyl)-
phenyl]-3-(difluoromethyl)-
- 20 146 1H-pyrazole-4-carboxamide, 1- 125
methyl-N-[2-(cycloheptylmethyl)-
phenyl]-3-(trifluoromethyl)-
- 147 1H-pyrazole-4-carboxamide, N-[2- 116
(cycloheptylidene(methyl)phenyl]-1-
methyl-3-(difluoromethyl)-
- 25 148 1H-pyrazole-4-carboxamide, N-[2-(3- 103-104
methyl-1-cyclopenten-1-yl)phenyl]-
1-methyl-3-(trifluoromethyl)-
- 30 149 1H-pyrazole-4-carboxamide, N-[2-(4- 92
methyl-1-cyclopenten-1-yl)phenyl]-
1-methyl-3-(difluoromethyl)-

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5 The compounds of the present invention may be used as is without adding any other components, but generally, they are formulated into emulsifiable concentrates, wettable powders, suspension formulations, granules, dusts, and the like by mixing with a solid or 10 liquid carrier, a surface active agent and other adjuvants for formulation. The compounds of the present invention may also be microencapsulated or otherwise formulated for delayed release of activity.

15 The content of a compound of the present invention contained as an active ingredient in these formulations is 0.1 to 99.9%, preferably 0.2 to 80% by weight, and more preferably 2 to 50% by weight. The concentration of the active compound in the spray solutions as they are applied to growing plants will be 20 much less, from about 10 ppm up to about 1000 ppm.

25 The exact amount of active ingredient per hectare to be employed in the treatment or prevention of disease is dependent upon various factors, including the plant species and stage of development of plants and disease, the amount of rainfall, and the specific adjuvants employed. In foliar applications a dosage of from about 10 to about 2000 g/ha, preferably from about 20 to about 250 g/ha, is usually employed. In soil applications a dosage of from about 100 to about 2000 g/ha, preferably 30 from about 250 to about 500 g/ha is usually employed. Lower or higher rates may be required in some instances. One skilled in the art can readily determine from this specification, including the following examples, the optimum rate to be applied in any particular case.

35 The solid carriers include, for example, fine powders or granules of kaolin clay, attapulgite clay, bentonite, acid clay, pyrophyllite, talc, diatomaceous earth, calcite, corn starch powder, walnut shell powder,

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urea, ammonium sulfate, synthetic hydrated silicon dioxide, and the like. The liquid carrier includes, for example, aromatic hydrocarbons such as xylene, methylnaphthalene and the like, alcohols such as

5 isopropanol, ethylene glycol, cellosolve and the like, ketones such as acetone, cyclohexanone, isophorone and the like, vegetable oils such as soybean oil, cotton seed oil and the like, dimethyl sulfoxide, acetonitrile, water, and the like.

10 The surface active agents used for emulsification, dispersion, wetting, etc, include, for example, anionic surface active agents, such as salts of alkyl sulfate, alkyl or aryl sulfonates, dialkylsulfosuccinates, salts of polyoxyethylene alkyl aryl ether 15 phosphoric acid esters, or naphthalenesulfonic acid/formalin condensates, etc, and nonionic surface active agents, such as polyoxyethylene alkyl ether, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, or polyoxyethylene sorbitan 20 fatty acid esters, etc. Other adjuvants for formulation include, for example, xanthan gum, lignosulfonates, alginates, polyvinyl alcohol, gum arabic, and CMC (carboxymethyl cellulose).

The compounds of the present invention may also 25 be combined with other fungicides, plant growth regulators, fertilizers, herbicides, and insecticides. Penetrating agents, to increase systemic activity may also be added to the compounds of the present invention.

Diseases for which the compounds of the present 30 invention may be used include, but are not limited to, those caused by species of *Rhizoctonia*, *Botrytis*, *Septoria*, *Alternaria*, *Cercosporidium*, *Pseudocercosporella*, *Monilinia*, *Sphaerotheca*, *Uncinula*, *Erysiphe*, *Puccinia*, and *Venturia*.

35 Crops on which the compounds may be used include, but are not limited to, cereals, for example, wheat, rye, barley, and rice; fruits, for example, apples and grapes; vegetables, for example, eggplants, cucumbers,

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and tomatoes; oil-producing crops, for example, peanuts, soybeans, and oilseed rape; and turf. Application methods to be used in fungal control on plants include, but are not limited to, direct application to the body
5 of the plant by spraying or other direct application means; soil treatment prior to or at the time of planting, or at any time during the life of the plant; and application to the seed or seed pieces prior to or at the time of planting. The latter two means expose
10 the rhizosphere of the plant to the treatment compound.

The compounds of the present invention have been tested for fungicidal effectiveness in a variety of tests. They have demonstrated exceptionally high levels of control of ascomycete disease such as *Botrytis* as
15 demonstrated in an enzyme inhibition test as well as in vivo tests. They also have good activity against *Rhizoctonia solani* as shown below. The compounds have been compared to carboxin and Compound No. 12 of U.S. Patent No. 4,134,987 (Huppertz, January 16, 1979), the
20 full text of which is incorporated herein by reference, believed to be the closest compound of the prior art. This known fungicide, N-(2-methylphenyl)-1,3,5-(trimethyl)-4-pyrazolecarboxamide, is hereinafter designated Compound H. The following examples describe
25 the tests conducted and the results thereof.

EXAMPLE 1

Enzyme Inhibition

Mitochondria were isolated by a method adapted
30 from G.A. White [Biochem. Biophys. Res. Commun. 44:
1212, 1971]. Twenty to thirty grams of *Botrytis cinerea* isolate Nick were resuspended in 250 mL 0.25M sucrose, 5mM Na₄EDTA, pH 7.0 (+) 0.15% (w/v) bovine serum albumin (BSA) and placed in a Bead Beater chamber (Biospec
35 Products, Bartlesville, OK). Zirconium oxide beads (0.5mm) were added to finish filling the chamber. Four 30 second beats separated by 2 minute temperature equilibration periods in the cold were used to break the

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mycelia. A crude mitochondrial preparation was harvested from the homogenate by differential centrifugation at 4 °C and resuspended in BSA-free sucrose/EDTA media and used for SDH assays.

- 5 The succinate dehydrogenase activity was measured at 600nm in 50mM potassium phosphate, pH 7.2, 1mM KCN, 45 μ M 2,6-dichlorophenolindophenol (DCPIP) and 17mM disodium succinate (final volume, 1mL) with a Perkin-Elmer Lambda 7 ultraviolet-visible spectrophotometer.
- 10 The test compounds were added as acetone solutions (final concentration of acetone, 1% (v/v)). The mitochondrial preparations were used to initiate the reaction. All rates were corrected for endogenous activities minus succinate. Semilog plots of percentage inhibition versus test compound concentration were used to determine inhibition expressed as I_{50} (μ M) which is the concentration required to inhibit the rate of DCPIP reduction by 50%. The commercial fungicide carboxin was used as standard throughout.
- 15 The results of this assay for the compounds of the present invention are reported in Table 1.

Table 1

<u>Example Number</u>	<u>I_{50} (μM conc.)</u>
1	0.0095
25 2	0.012
3	0.027
4	0.065
5	0.0066
6	0.25
30 7	0.0072
8	0.016
9	0.0019
10	0.003
11	0.0054
35 12	0.0089
13	0.011
14	0.29
15	0.014

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	16	0.024
	17	0.0063
	18	0.031
	19	0.028
5	20	0.014
	21	0.019
	22	0.0071
	23	0.01
	24	0.0012
10	25	0.0011
	26	0.0017
	27	0.0048
	28	0.01
	29	0.036
15	30	0.34
	31	0.068
	32	0.11
	33	0.0014
	34	0.0059
20	35	0.012
	36	0.021
	37	0.0048
	38	0.014
	39	0.36
25	40	0.079
	41	0.021
	42	0.2
	43	0.38
	44	0.052
30	45	0.092
	46	0.096
	47	0.16
	48	0.02
	49	0.047
35	50	0.098
	51	0.023
	52	0.049
	53	0.021

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	54	0.011
	55	0.027
	56	0.013
	57	0.0047
5	58	0.0086
	59	1
	60	0.35
	61	0.19
	62	0.29
10	63	0.0063
	64	0.047
	65	0.011
	66	0.048
	67	0.056
15	68	0.0037
	69	0.033
	70	0.012
	71	0.046
	72	0.031
20	73	0.0076
	74	0.090
	75	0.013
	76	0.032
	77	22
25	78	8.7
	79	0.011
	80	0.083
	81	0.38
	82	0.065
30	83	0.13
	84	0.013
	85	0.01
	86	0.0063
	87	0.059
35	88	0.035
	89	0.021
	90	0.79
	91	0.078

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	92	0.062
	93	0.044
	94	0.074
	95	0.64
5	96	0.43
	97	0.59
	98	0.8
	99	0.065
	100	0.19
	101	1.4
10	102	16
	103	0.52
	104	0.77
	105	0.26
	106	0.094
	107	0.055
15	108	1.6
	109	0.0072
	110	0.019
	111	0.0038
	112	0.0021
	113	0.013
20	114	0.0036
	115	0.0065
	116	0.048
	117	0.17
	118	0.029
	119	0.0035
25	120	0.0041
	121	0.0069
	122	0.034
	123	0.023
	124	0.013
	125	0.005
30	126	0.0066
	127	0.083
	128	1.3
	129	0.11

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	130	0.37
	131	0.19
	132	0.0035
	133	0.0046
5	134	0.0047
	135	0.01
	136	**
	137	0.02
	138	0.13
	139	0.032
10	140	0.039
	141	0.049
	142	0.22
	143	0.025
	144	0.037
15	145	0.025
	146	0.053
	147	0.02
	148	0.027
	149	0.013
20	150	0.026
	Carboxin	*0.72 ± 0.3
	Compound H	475

*Average of 24 determinations.

25 ** Not determined due to limited solubility in
medium.

EXAMPLE 2**Eggplant grey mold**

30 Eggplant seeds are planted in 2.25" square pots,
six per pot, and maintained in growth chambers set at 23
°C, 80% humidity, and 12 h photoperiod. When the plants
are at the cotyledon stage (14-18 days after planting),
the plants are sprayed with 1.5 mL/pot of 500, 100 or 20
35 ppm 2:3 acetone:water (with 0.5% Tween® 20) formulations
of the test compounds.

Twenty-four hours later the plants are inoculated
with *Botrytis cinerea*, approximately 0.5 mL/pot of a 4 x

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10^6 spores/mL suspension. The plants are incubated at 23 °C and 100% humidity for 3-4 days, at which time disease control ratings are made based on presence and severity of *Botrytis* lesions. The ratings use the following scale:

- 0 = No disease control
- 1 = Low level of control
- 2 = Moderate control
- 3 = High level of control

10 The results of this test for compounds of the present invention are reported in Table 2.

Table 2

	<u>Compound Number</u>	<u>Disease Control Rating at 500/100/20 ppm</u>
15	1	3/3/3
	2	3/3/1
	3	2/1/0
	4	2/2/1
	5	3/3/1
20	6	1/-/-
	7	0/-/-
	8	0/-/-
	9	2/2/0
	10	2/2/2
25	11	3/2/2
	12	3/1/1
	13	3/1/1
	14	0/-/-
	15	2/3/2
30	16	1/-/-
	17	2/2/1
	18	0/-/-
	19	3/2/1
	20	3/2/1
35	21	2/2/1
	22	0/-/-
	23	0/-/-
	24	2/2/1

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	25	2/2/1
	26	1/2/1
	27	2/1/0
	28	2/1/0
5	29	0/-/-
	30	2/2/0
	31	0/0/0
	32	2/1/0
	33	2/1/1
10	34	2/2/0
	35	3/3/2
	36	0/-/-
	37	2/0/0
	38	2/2/0
15	39	1/-/-
	40	1/0/0
	41	3/0/0
	42	0/-/-
	43	0/-/-
20	44	1/-/-
	45	0/-/-
	46	0/-/-
	47	0/-/-
	48	0/-/-
25	49	0/-/-
	50	0/-/-
	51	0/-/-
	52	0/-/-
	53	0/-/-
30	54	0/-/-
	55	0/-/-
	56	0/-/-
	57	0/-/-
	58	2/0/0
35	59	0/-/-
	60	0/-/-
	61	1/-/-
	62	1/0/0

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	63	1/-/-
	64	2/1/1
	65	2/1/0
	66	2/0/0
5	67	2/1/0
	68	1/-/-
	69	0/-/-
	70	3/2/1
	71	0/-/-
10	72	0/-/-
	73	0/-/-
	74	1/0/0
	75	0/-/-
	76	0/-/-
15	77	2/1/0
	78	2/1/1
	79	2/1/0
	80	0/-/-
	81	0/-/-
20	82	0/-/-
	83	2/0/0
	84	2/1/0
	85	2/1/0
	86	0/-/-
25	87	0/-/-
	88	0/-/-
	89	0/-/-
	90	0/0/0
	91	0/-/-
30	92	0/-/-
	93	0/0/0
	94	0/-/-
	95	0/-/-
	96	0/-/-
35	97	1/0/0
	98	0/-/-
	99	1/-/-
	100	0/-/-

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	101	0/-/-
	102	1/-/-
	103	0/-/-
	104	0/-/-
5	105	1/0/0
	106	0/-/-
	107	0/-/-
	108	0/-/-
	109	0/-/-
10	110	2/2/1
	111	1/1/1
	112	3/3/2
	113	3/1/1
	114	2/1/0
15	115	3/2/1
	116	1/0/0
	117	2/1/0
	118	0/-/-
	119	2/1/0
20	120	2/0/0
	121	1/0/0
	122	2/2/1
	123	0/0/0
	124	2/1/0
25	125	2/1/2
	126	1/1/0
	127	1/0/0
	128	0/0/0
	129	0/0/0
30	130	0/0/0
	131	0/0/0
	132	0/-/-
	133	1/0/0
	134	2/1/1
35	135	2/1/1
	136	1/0/0
	137	3/3/1
	138	0/0/0

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	139	0/0/0
	140	1/1/0
	141	1/0/0
	142	1/1/0
5	143	0/0/0
	144	1/0/0
	145	0/0/0
	146	1/0/0
	147	0/0/0
	148	2/2/0
	149	1/0/0
10	150	2/0/0
	Carboxin	0/-/-
	Compound H	0/-/-

15 - = no test

EXAMPLE 3

Vine grey mold

Grape berries, which have been washed and surfaced sterilized in 70% ethanol for one minute, are, except for the negative controls, treated with 0.2 mL of a 2:3 acetone/water formulation (containing 0.05% Tween® 20) of 200 or 50 ppm of the test compounds and placed one per well in 12-well plates. Six berries per treatment level are used. Twenty-four hours later each berry is inoculated with *Botrytis cinerea* conidia, 0.2 mL of 10^6 spores/mL suspension. The plates are incubated at 20 °C with a 12 hour photoperiod for 7-10 days and the percent surface area infected with the disease is determined for each replicate using the values of 0, 1, 2, 5, 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, and 100%. Treatment means are calculated and percent disease control is determined by the formula [(control mean - treatment mean) / control mean] × 100.

The results of this test, reported as the average of six berries per treatment level are shown in Table 3. Some of the compounds have been tested more than once

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and the results shown are the average of the number of tests reported.

Table 3

		<u>% DISEASE CONTROL</u>	
		<u>200 ppm</u>	<u>50 ppm</u>
		<u>COMPOUND NUMBER</u>	
5	1	94*	92*
	2	87*	84*
	3	62	10
10	4	58*	29
	5	40*	50*
	6	20	0
	7	86*	72*
	8	83	37
15	9	89*	94*
	10	85*	87*
	11	92*	75*
	12	59	58
	13	66*	63*
20	14	0	0
	15	89*	36*
	16	57	15
	17	95*	90*
	18	0	0
25	19	52	32
	20	81*	78*
	21	34*	40*
	22	22	24
	23	66	20
30	24	100	87*
	25	78*	66*
	26	100*	97*
	27	74*	80*
	28	77	37
35	29	54	0
	30	59*	75
	31	23	0
	32	5	6

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	33	41	34
	34	11	44
	35	46	42
	36	38	14
5	37	54	25
	38	14	0
	39	55	50
	40	3	2*
	41	37	34*
10	42	25	0*
	43	0	3*
	44	37	0*
	45	12	7*
	46	0	1*
15	47	0	3*
	48	0	10*
	49	0	4*
	50	22	8*
	51	27	16*
20	52	30	19*
	53	70	40*
	54	2	2*
	55	0	11*
	56	70	46*
25	57	72	53*
	58	78	51*
	59	0	0
	60	0	0
	61	0	0*
30	62	0	0
	63	65	34*
	64	28	10*
	65	85	47*
	66	35	32*
35	67	0	31*
	68	89	78
	69	70	30
	70	96*	97*

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	71	57	25*
	72	0	0*
	73	0	8*
	74	0	4*
5	75	0	6*
	76	0	8*
	77	82	85
	78	35	35
	79	97	69
10	80	0	0
	81	7	0
	82	0	0
	83	55	56*
	84	96	93*
15	85	99	28
	86	82	66
	87	46*	61*
	88	0	0
	89	13	24
20	90	33	0
	91	14	0
	92	30	36
	93	15	0
	94	0	0
25	95	26	48
	96	0	0
	97	1	0
	98	0	14
	99	53	27
30	100	22	0
	101	16	10
	102	83*	88*
	103	18	5
	104	48	0
35	105	0	6
	106	3	9
	107	49	27
	108	0	12

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	109	100	100*
	110	100	97*
	111	100	99*
	112	95	88*
5	113	60	28
	114	90	78*
	115	95	42*
	116	68	21
	117	19	80
10	118	87	37
	119	84	73
	120	82	60
	121	64	33
	122	79*	67*
15	123	36	14
	124	96	48
	125	93	88*
	126	97	59*
	127	52	12
20	128	0	0
	129	0	7
	130	21	2
	131	0	7
	132	51*	50*
25	133	36	39
	134	61*	66*
	135	66	52
	136	0	7
	137	100	83*
30	138	4	0
	139	1	2
	140	12	16
	141	12	12
	142	18	0
35	143	36	33
	144	37	15
	145	0	0
	146	0	0

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	147	0	0
	148	99	37
	149	100	95
	150	100	40
5	Carboxin	0	0
	Compound H	9*	5*

- = no test

* The result reported is the average of
more than one test.

10

EXAMPLE 4

Rice sheath blight.

Rice plants, 11 to 15 days old, are grown in 7.65 cm² pots. Each plant in the treatment groups is treated 15 by spraying both the foliage and the soil surface, each with 2 mL of a water/acetone/Tween®20 formulation containing 0.5, 0.1, or 0.02 mg/mL of Compound A. The pots are placed in flood trays which are filled with water to just below the soil line. Two days later, 20 approximately two grams of *Rhizoctonia solani* inoculum, cultured on rice grain for four to eight weeks, is applied to the base of the rice plants in each pot. After 7 days in a 25 °C high humidity growth chamber, each plant is evaluated for the level of disease control 25 as compared to untreated controls by the following scale and the average of five plants per treatment level is calculated.

0 = No disease control

1 = Low level of disease control

30 2 = Moderate disease control

3 = High level of disease control

The results of this test for compounds of the present invention are reported in Table 4.

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Table 4

<u>Compound Number</u>	<u>Disease Control Rating at 0.5/0.1/0.02 mg/mL</u>
5	1 0/0/2
	2 3/3/3
	3 0/-/-
	4 0/-/-
	5 0/-/-
10	6 1/0/0
	7 1/-/-
	8 0/-/-
	9 3/3/3
	10 3/3/2
15	11 3/3/1
	12 2/-/-
	13 3/3/2
	14 1/-/-
	15 0/-/-
20	16 1/-/-
	17 3/-/-
	18 0/-/-
	19 3/3/1
	20 3/3/2
25	21 1/-/-
	22 0/-/-
	23 3/2/1
	24 3/3/3
	25 1/-/-
30	26 1/-/-
	27 0/-/-
	28 0/-/-
	29 0/-/-
	30 3/3/2
35	31 1/-/-
	32 0/-/-
	33 3/1/1
	34 3/3/2
	35 3/3/2

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	36	0/-/-
	37	3/3/3
	38	1/0/0
	39	0/-/-
5	40	0/-/-
	41	3/3/1
	42	3/3/2
	43	3/3/2
	44	0/-/-
10	45	0/-/-
	46	3/3/2
	47	3/3/1
	48	2/-/-
	49	0/-/-
15	50	2/0/0
	51	2/1/0
	52	2/2/0
	53	3/3/2
	54	2/-/-
20	55	0/-/-
	56	0/-/-
	57	0/-/-
	58	2/-/-
	59	0/-/-
25	60	0/-/-
	61	0/-/-
	62	0/-/-
	63	3/3/2
	64	3/3/1
30	65	3/3/2
	66	3/3/3
	67	2/-/-
	68	3/3/2
	69	3/2/0
35	70	0/-/-
	71	3/3/1
	72	0/-/-
	73	2/-/-

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	74	0/-/-
	75	0/-/-
	76	0/-/-
	77	0/-/-
5	78	0/-/-
	79	3/3/3
	80	3/3/2
	81	3/3/3
	82	3/3/3
10	83	3/3/3
	84	0/-/-
	85	3/3/1
	86	3/3/3
	87	2/-/-
15	88	0/-/-
	89	0/-/-
	90	0/-/-
	91	0/-/-
	92	2/1/0
20	93	0/-/-
	94	0/-/-
	95	0/-/-
	96	0/-/-
	97	0/-/-
25	98	0/-/-
	99	3/3/2
	100	2/1/0
	101	3/1/0
	102	3/3/3
30	103	0/-/-
	104	0/-/-
	105	0/-/-
	106	3/3/2
	107	3/3/1
35	108	0/-/-
	109	3/1/0
	110	3/0/0
	111	3/3/3

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	112	0/-/-
	113	3/3/3
	114	3/3/3
	115	3/3/3
5	116	3/1/1
	117	0/-/-
	118	1/-/-
	119	2/-/-
	120	3/-/-
10	121	3/3/1
	122	0/-/-
	123	0/-/-
	124	2/-/-
	125	3/2/2
15	126	3/-/-
	127	2/-/-
	128	0/-/-
	129	3/3/3
	130	2/-/-
20	131	2/-/-
	132	3/2/1
	133	3/2/1
	134	3/3/3
	135	3/-/-
25	136	0/-/-
	137	3/2/1
	138	2/-/-
	139	3/2/2
	140	3/2/0
30	141	3/-/-
	142	3/-/-
	143	3/-/-
	144	3/-/-
	145	3/-/-
35	146	1/-/-
	147	2/-/-
	148	3/-/-
	149	3/-/-

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150	3/-/-
Carboxin	3/1/0
Compound H	0/-/-

- = no test

5

Field Tests

- The compounds of Examples 1-150 are combined with various adjuvants, carriers, and other additives and applied to vineyards at rates of from 0.01 to 2.0 kg
- 10 active ingredient per hectare which reduce the incidence of *Botrytis* compared to untreated fields. The compounds in mixture with various adjuvants, carriers, and other additives are also applied to various vegetables and cereals at rates of from 0.01 to 2.0 kg active
- 15 ingredient per hectare and reduce the incidence of fungal disease compared to untreated fields.

COMPOSITION EXAMPLES

		<u>Wt.Pct.</u>
Suspension Concentrate:		<u>Wt.Pct.</u>
20	Compound No. 40	48.900
	Polyoxypropylene-polyoxyethylene block copolymer	2.550
	Sodium Lignin Sulfonate	2.040
	10% Dimethylpolysiloxane Emulsion	1.020
25	1% Xanthan gum solution	0.990
	Water	44.500
Emulsifiable Concentrate:		<u>Wt.Pct.</u>
30	Compound No. 26	13.5
	Ethoxylated sorbitan (20EO)	5.0
	C9 Aromatics	81.5
Wettable Powder:		<u>Wt.Pct.</u>
35	Compound No. 12	75.0
	Sodium lignin sulfonate	3.0
	Sodium N-methyl-N-oleyl-taurate	1.0
	Kaolinite clay	21.0

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Granule:	<u>Wt.Pct.</u>
Compound No. 5	1.0
Propylene glycol	5.0
Montmorillonite (24/48 mesh)	94.0
5	
Dust:	<u>Wt.Pct.</u>
Compound No. 15	50.0
Graphite	10.0
Kaolinite clay	40.0
10	

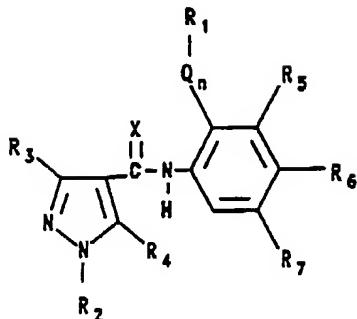
While the illustrative embodiments of the invention have been described with particularity, it will be understood that various other modifications will be apparent to and can be readily made by those skilled in the art without departing from the spirit and scope of the invention. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the examples and descriptions set forth hereinabove but rather that the claims be construed as encompassing all 15 the features of patentable novelty which reside in the present invention, including all features which would be treated as equivalents thereof by those skilled in the art to which the invention pertains.

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CLAIMS:

1. A compound of the formula:

5



10

wherein:

Q is C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl,

$-(CH_2)_mCH=$, or $-(CH_2)_m-X-(CH_2)_m-$;

n is 0 or 1;

15 each m is independently 0, 1, 2, or 3;

each X is independently O or S;

R₁ is C3-C12 cycloalkyl, C3-C12 cycloalkenyl, C6-C12

bicycloalkyl, C3-C12 oxacycloalkyl, C3-C12

oxacycloalkenyl, C3-C12 thiacycloalkyl, C3-C12

20 thiacycloalkenyl, or C3-C12 cycloalkylamine, each
of which may be optionally substituted with one
or more C1-8 alkyl, C1-8 alkoxy, halo, or cyano
groups, provided that when -Q-R₁ is $-(CH_2)_mCH=R_1$,
the cycloalkyl of R₁ is a cycloalkylidene;

25 R₂ is hydrogen, fluorinated methyl, methyl, ethyl, C2-C6
alkenyl, C3-C6 cycloalkyl, phenyl,
alkylthioalkyl, alkoxyalkyl, haloalkylthioalkyl,
haloalkoxyalkyl, or hydroxylalkyl;

30 R₃ is halomethyl, halomethoxy, methyl, ethyl, halo,
cyano, methylthio, nitro, aminocarbonyl, or
aminocarbonylmethyl;

R₄ is hydrogen, halo, or methyl;

35 R₅, R₆, and R₇ are each independently selected from
hydrogen, halo, cyano, C1-6 alkyl, C2-C6 alkenyl,
C2-C6 alkynyl, C1-C4 alkoxy, C1-C4 alkylthio, C3-
C4 cycloalkyl, and halomethoxy.

2. The compound of Claim 1 wherein R₄ is hydrogen
and R₃ is fluorinated methyl.

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3. The compound of Claim 2 wherein n is 0 and R₁ is C6-C12 cycloalkyl.
4. The compound of Claim 2 wherein n is 0 and R₁ is C6-C12 bicycloalkyl.
5. Fungicidal compositions comprising a compound of Claim 1 and an adjuvant.
6. The fungicidal composition of Claim 5 wherein in said compound R₄ is hydrogen and R₃ is fluorinated methyl.
- 10 7. The fungicidal composition of Claim 6 wherein in said compound n is 0 and R₁ is C6-C12 cycloalkyl.
8. The fungicidal composition of Claim 6 wherein in said compound n is 0 and R₁ is C6-C12 bicycloalkyl.
9. A method of controlling fungal disease of a plant
15 comprising applying a compound of Claim 1 to the plant locus.
10. The method of Claim 9 wherein in said compound R₄ is hydrogen and R₃ is fluorinated methyl.
11. The method of Claim 10 wherein in said compound n
20 is 0 and R₁ is C6-C12 cycloalkyl.
12. The method of Claim 10 wherein in said compound n is 0 and R₁ is C6-C12 bicycloalkyl.
13. The method of Claim 9 wherein said plant locus is the foliage of said plant.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/10509

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07D231/14;	A01N43/56;	C07D231/16;	C07D231/18
C07D231/22;	C07D409/12;	C07D405/12	

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	C07D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No ¹³
X	FR,A,2 337 997 (COMMONWEALTH SCIENTIFIC AND INDUSTRIALRESEARCH ORGANIZATION) 1977 see claim 1; table 1 & US,A,4 134 987 cited in the application ---	1-13
A	EP,A,0 199 822 (SUMITOMO CHEMICAL COMPANY LIMITED) 5 November 1986 see page 1 & US,A,4 742 074 cited in the application ---	1-13
A	EP,A,0 368 749 (SUMITOMO CHEMICAL COMPANY LIMITED) 16 May 1990 ---	-/-

¹⁰ Special categories of cited documents :¹⁰

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IV. CERTIFICATION

Date of the Actual Completion of the International Search

04 MARCH 1993

Date of Mailing of this International Search Report

17. 03. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

DE JONG B.S.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	WO,A,9 212 970 (MONSANTO COMPANY) 6 August 1992 see claims -----	1-13

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9210509
SA 68022

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 04/03/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	1077048	06-05-80
		DE-A-	2701091	28-07-77
		GB-A-	1573942	28-08-80
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